



DERMIK LABORATORIES, INC.

Dedicated to Dermatology

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October 12, 1999

Janet Woodcock, M.D.
Center for Drug Evaluation and Research
Office of the Center Director
HFD-001
Food and Drug Administration
Woodmont Office Complex 2
1451 Rockville Pike, Room 6027
Rockville, MD 20852

OCT 13 1 22 PM '99

Docket No 98D-0388

**Draft Guidance for Industry on Topical Dermatological
Drug Product NDA's and ANDA's - In Vivo
Bioavailability, Bioequivalence, In Vitro Release and
Associated Studies**

Dear Dr. Woodcock:

The purpose of this letter is to bring to your attention a substantial and very serious problem related to the above mentioned Draft Guidance that, if it is not resolved, will result in inconsistent and unfair decisions within CDER relating to pioneer and generic dermatologic drugs. Although this Draft Guidance has been under discussion for at least one year, no consensus has been reached among the concerned Divisions at FDA, Industry, and Academic Experts.

Specifically, it has come to Dermik's attention that the Deputy Director for Pharmaceutical Sciences, intends to finalize the above noted Draft Guidance despite the fact that serious concerns raised by the Director of the Division of Dermatologic and Dental Drug Products (DDDDP), members of the FDA Expert Panel on Dermatopharmacokinetics (DPK) and members of the Dermatologic and Ophthalmic Drugs Advisory Committee have not been resolved. If this Draft Guidance is finalized as proposed, generic drug products will be subject to different standards than the pioneer drug products, which will result in substantial inequity.

It is the position of Dermik Laboratories, Inc. that, since there is no consensus among FDA's scientists or the Expert Advisors, and because there are a number of technical issues raised at the Joint Advisory Committee Meetings that have not been adequately addressed, this Draft Guidance should not be finalized at this time. Dermik's concerns and general objections with the current Draft Guidance are fully expressed in Attachment I.

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Janet Woodcock, M.D.

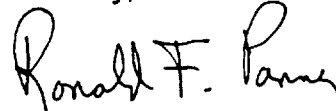
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We, therefore, ask that you take steps to assure that this Draft Guidance not be issued until it is more adequately considered, the relevant scientific issues are resolved, and whatever standards are set forth can be assured to apply uniformly and consistently to both pioneer and generic dermatological drugs.

Dermik Laboratories, Inc. is appreciative of your attention and consideration of this important issue.

Sincerely,

A handwritten signature in black ink, appearing to read "Ronald F. Panner". The signature is fluid and cursive, with the first name "Ronald" being more prominent.

Ronald F. Panner

Senior Director

WorldWide Regulatory Affairs

cc:

Dr. R. Williams

Dr. V. Shah

Dr. J. Wilkin

Dr. R. DeLap

Mr. J. Morrison

Dr. J. Henney

Dr. M. Lumpkin

Dr. R. Temple

Mr. S. Unger

ATTACHMENT I

Dermik Laboratories, Inc., is a wholly owned subsidiary of Rhône-Poulenc Rorer, Inc. and is engaged in the research, development, manufacture and sale of prescription and non-prescription topical drug products. Dermik is the holder of approved New Drug Applications for topical dermatological drug products, and has a direct interest in the Draft Guidance for industry entitled "*Topical Dermatological Drug Product NDA's and ANDA's - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies*" which was announced in the June 18, 1998 Federal Register. This Draft Guidance proposes that an ANDA for a topical drug product can be approved based upon a purported showing of bioequivalence to the innovator product through dermatopharmacokinetic (DPK) studies. In the proposed DPK method, successive layers of the outermost skin, the stratum corneum, are 'stripped' with tape so that drug concentrations may be measured.

This Draft Guidance was the subject of a joint meeting of the Advisory Committee for Pharmaceutical Science and the Dermatologic and Ophthalmic Drugs Advisory Committee (ACPS/DODAC) in October, 1998. There was disagreement among FDA scientists and no panel agreement or consensus at that meeting. It has come to our attention that in the August 24, 1999 meeting of the Expert Panel on DPK, FDA's Deputy Center Director for Pharmaceutical Science communicated that, despite the continuing scientific disagreement about the Draft Guidance, it will be finalized in the near future.

It is Dermik's position this Draft Guidance should not be finalized at this time, and that FDA should not approve any ANDA for a topical dermatological drug product based upon purported demonstration of bioequivalence consistent with the methods and principles outlined in the Draft Guidance. Our general objections are that, in its current form, the Draft Guidance;

- does not require a generic drug product to be qualitatively the same as the reference drug,
- does not represent consensus among the concerned FDA scientists, or their expert advisors,
- does not sufficiently address technical issues validating the proposed DPK methodology as suitable for the demonstration of bioequivalence of topical drug products.

Dermik's concerns are more fully expressed below.

1. The Draft Guidance in its most recent form could allow for material differences in product composition between generic and innovator drug products.

FDA's Deputy Center Director for Pharmaceutical Science and the Chair of the Topical Dermatological Drug Products Working Group proposed that DPK be used as a surrogate for bioequivalence when test and reference product are "qualitatively (Q1) same and/or functionally similar" (emphasis added), and should be quantitatively (Q2) similar to $\pm 10\%$. The SUPAC-SS approach is cited as the basis for this recommendation.

Dermik objects to this recommendation. DPK has yet to demonstrate correlation to clinical efficacy and safety of topical skin products, which are determined by both active ingredient and vehicle (excipients)^{1,2,3}. The test and reference product must be qualitatively identical (Q1); being "functionally similar", as proposed, is not appropriate. In addition, the proposed quantitative (Q2) range of $\pm 10\%$ is too broad. While $\pm 10\%$ is consistent with limits defined in SUPAC-SS, the premise behind SUPAC-SS is to reduce regulatory burden on a company that is making a defined change to a product for which a significant body of information has been established. The comparison of "Test" and "Reference" products manufactured by different firms, at different sites, by different processes, is beyond the defined scope of SUPAC-SS. A more appropriate limit on quantitative differences between generic and innovator products is $\pm 5\%$, as defined in the Interim Policy on Inactive Ingredients. The Interim Policy was revoked by FDA with the publication of a notice in the April 30, 1999 Federal Register (64FR 23340-23341). Once finalized, the current Draft Guidance will, in effect, replace the Interim Policy.

2. The Draft Guidance in its most recent form does not represent the thinking of the Agency or of its Advisory Committees, and will create disparate regulatory standards between generic and pioneer drug products.

There is no consensus among FDA's scientists or its expert advisors that the Draft Guidance should be finalized. The current proposal does not address the issues raised by the Director of the Division of Dermatologic and Dental Drug Products (DDDDP) at the October 1998 Joint Advisory Committee Meeting. At that meeting, the Director challenged the assumptions upon which DPK is based, and concluded that "stratum corneum is not the same thing as skin". He concluded that the Draft Guidance should be withdrawn. At the same meeting, representatives of the Dermatologic and Ophthalmic Drugs Advisory Committee expressed serious reservations about adopting the DPK methodology for the establishment of bioequivalence. Additionally, the Draft Guidance does not address the concerns raised by members of the Advisory Committee, including demonstration that DPK is relevant to diseased skin, and that the method is appropriately validated.

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If the Draft Guidance is finalized as proposed, generic drug products will be subject to disparate standards from the pioneer drug products. Currently, changes in Q1 and/or Q2 for innovator drug products may require additional safety studies, e.g. phototoxicity and photocarcinogenicity, that are not addressed in the current Draft Guidance. Innovator companies have been told by FDA's Division of Dermatologic and Dental Drug Products that it is required to conduct photocarcinogenicity studies for line-extension topical products which have changes to the formulation. The regulatory standards for the photobiology data requirements associated with topical drug product formulation changes must be consistent between the Office of Generic Drugs and the Division of Dermatologic and Dental Drug Products.

3. The DPK methodology is not validated to a suitable scientific standard to accept its use for regulatory purposes.

An overriding issue is whether the variability arising from multiple sources (excess drug removal, skin site variability, inter- and intra-subject variability, intra and inter-investigators, etc.) is so large and unmanageable as to call the entire method into question. The DPK methodology should not be accepted for the establishment of bioequivalence until there is validation not only of the precise procedure, but a demonstration that the DPK method is a consistently reliable, precise and accurate predictor of clinical safety and efficacy for each particular class of compounds, and disease state. This includes studies of mass balance. The Draft Guidance proposes additional studies to address these issues. In order to ensure that a valid method will be defined by the Draft Guidance, and ultimately used to approve new drug products, the additional studies proposed should be conducted prior to finalization of the Draft Guidance.

References:

1. J. Wilkin, FDA, Presentation during Joint Meeting of the Advisory Committee for Pharmaceutical Science and Dermatologic and Ophthalmic Drugs Advisory Committee, October 23, 1998.
2. Jamouille, JC and Schaefer, H., "Cutaneous bioavailability, bioequivalence and percutaneous absorption. In vivo methods, problems and pitfalls" In: Topical Drug Bioavailability, Bioequivalence and Penetration ed. by VP Shah and HI Maibach, pp129-153, 1993.
3. Jacobs A., Avalos J., Brown P., and Wilkin J., Does Photosensitivity Predict Photocarcinogenicity? Int. J. Toxicology, 18:191-198, 1999.